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ON STOCHASTICITY IN THE VON FOERSTER HYPERBOLIC PARTIAL DIFFERENTIAL EQUATION SYSTEM

FURTHER APPLICATIONS TO THE MODELING OF AN ASYNCHRONOUSLY DIVIDING CELLULAR SYSTEM

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Abstract—We investigate the problem of including stochastically varying components in the Von Foerster hyperbolic partial differential equation system. In particular, we address the incorporation of stochasticity in the birth and death rates of the model. We assume, for the purposes of this analysis, that the stochasticity is slowly varying. The results of this analysis have bearing upon the modeling of biological populations which have a describable age-time dynamics. This analysis also has bearing upon some recent results concerning the modeling of asynchronously dividing cellular systems.

1. INTRODUCTION AND PRELIMINARIES

The history of mathematical models involving age-time distribution is well documented by a number of authors[1, 2]. Although a number of researchers pre-dated his work, the work of Von Foerster[3] constitutes the classic paper and the age-time structure for population models usually bears his name. For a historical review from an epidemiological standpoint see Hoppensteadt[1] and from a cellular standpoint see Witten[2].

We will not derive the Von Foerster system, this may be found in Hoppensteadt[1]. The classic Von Foerster system is given by

$$n_t + n_a = -\mu(t, a)n$$

$$n(0, a) = n_0(a) \tag{1.1}$$

$$n(t, 0) = \int_0^\infty \lambda(t, a)n(t, a)\,da$$

where $n(t, a)$ is the density of individuals of age a at time t, $\lambda(t, a)$ is the fertility function, and $\mu(t, a)$ is the mortality function. The solution to this system of equations can be shown to be

$$n(t, a) = \begin{cases} n_0(a - t)\exp\left[-\int_0^t \mu(a - t + \sigma, \sigma)\,d\sigma\right] & t < a \\ B(t - a)\exp\left[-\int_0^a \mu(\sigma, t - a + \sigma)\,d\sigma\right] & t > a \end{cases} \tag{1.2}$$

where $B(t)$ satisfies the integral equation

$$B(t) = f(t) + \int_0^t K(t, a)B(t - a)\,da$$

and

$$f(t) = \int_t^\infty \lambda(t, a) m(t, a) n_0(a - t)\, da$$

$$m(t, a) = \exp\left[- \int_0^t \mu(a - t + \sigma, \sigma)\, d\sigma \right] \tag{1.3}$$

$$K(t, a) = \lambda(t, a) k(t, a)$$

$$k(t, a) = \exp\left[- \int_0^a \mu(\sigma, t - a + \sigma)\, d\sigma \right].$$

These solutions are discussed in Hoppensteadt[1]. However, an elegant derivation and a very lucid discussion may be found in Trucco[4].

The dynamics of (1.1) has been studied by numerous investigators under a wide variety of assumptions and constraints. The literature is far too vast to review here. The thrust of this body of literature is however the consideration of nonstochastic μ and λ functions.

In this paper we consider the introduction of stochastically varying $\mu(t, a)$ and $\lambda(t, a)$ as a natural extension of the work on Von Foerster systems. In the upcoming section, we consider the incorporation of a stochastically varying mortality $\mu(t, a)$.

2. STOCHASTICALLY VARYING MORTALITY

Fluctuation in biological populations can arise through a number of contributing factors. In homogeneous age populations, this fluctuation may occur due to fluctuations in environmental terms (environmental carrying capacity) or due to fluctuations in the net growth rate terms. It is natural, then, to consider how contributions to fluctuation might occur in equation (1.1).

Since we do not directly incorporate environmental contributions in (1.1), the only source for stochastic variation arises in the components $\mu(t, a)$ and $\lambda(t, a)$ (the growth rate terms). It is natural, then, to consider that the death rate is deterministic in age but stochastic in time in such a manner as to be describable in the form

$$\mu(t, a) = \mu_1(a)\mu_2(t) \tag{2.1}$$

where $\mu_1(a)$ is a deterministic function of age and $\mu_2(t)$ is a stochastic function of time. In the upcoming discussion we will restrict ourselves to a particular choice for a class of functions $\mu_2(t)$.

Let t_k be an increasing sequence of times $k = 0, 1, 2, \ldots$; not necessarily equally spaced and chosen small enough such that $\mu_2(t)$ is a constant $\mu_2(t_k)$ on the interval $I_k = [t_k, t_{k+1})$. This constraint places the restriction, on our functions $\mu_2(t)$, of not varying too rapidly. Assuming $\mu_2(t)$ satisfies this constraint, let t_k^+, t_k^- be an increasing sequence of time points such that

$$\begin{aligned} &\lim_{t \downarrow t_k^+} n(t_k^+, a) = n(t_k, a) \\ &\lim_{t \uparrow t_k^-} n(t_k^-, a) = n(t_k, a). \end{aligned} \tag{2.2}$$

as illustrated in Fig. 1. Then, on the interval $I_k^+ = [t_k^+, t_{k+1}^-]$, $\mu_2(t) = \mu_2(t_k)$ and the dynamics of the system is governed by

$$n_t + n_a = -\mu(t_k) n \quad t \in I_k^+. \tag{2.3}$$

The new initial population, at time t_k^+, namely $n(t_k^+, a)$, is just $n(t_k^-, a)$. Further, the total

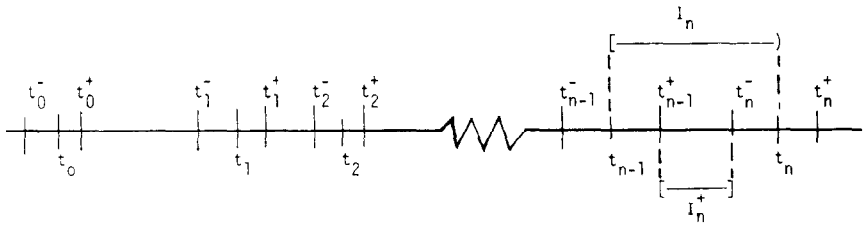

Fig. 1. An illustration of the time axis decomposition into the points t_k^-, t_k, t_k^+.

number of births—$B(t)$—remains $B(t)$. Hence, we obtain the new (1.1) system given by

$$\begin{cases} n_t + n_a = -\mu(t_k)n(t,a) \\ n(t_k^+, a) = n(t_k^-, a) \quad t \in I_k^+. \\ n(t,0) = \int_0^\infty \lambda(t,a,n)n(t,a)\,da. \end{cases} \tag{2.4}$$

If we replace our condition on $n(t_k^+, a)$ with the more general condition

$$n(t_k^+, a) = f[n(t_k^-, a)] \tag{2.5}$$

then we obtain the concept of a sequential–dynamical partial differential equation system [5–7].

Following the discussion of Trucco[4] and integrating along the characteristics ξ_k (as illustrated in Fig. 2) we obtain the solution for $n(t,a)$ on I_k^+

$$n(t,a) = \begin{cases} B(t-a-t_k^+)\exp\left[-\int_0^a \mu(t-a-t_k^+ + \sigma, \sigma)\,d\sigma\right] & t - t_k^+ > a \\ n(t_k^+, a)\exp\left[-\int_{t_k^+}^t \mu(\sigma - t_k^+, \sigma - a - t)\,d\sigma\right] & t - t_k^+ < a. \end{cases} \tag{2.6}$$

Replacing (2.5) into (2.6), we obtain the new solution system given by

$$n(t,a) = \begin{cases} B(t-a-t_k^+)\exp\left[-\int_0^a \mu(t-a-t_k^+ + \sigma, \sigma)\,d\sigma\right] & t - t_k^+ > a \\ f[n(t_k^-, a)]\exp\left[-\int_{t_k^+}^t \mu(\sigma - t_k^+, \sigma - a - t)\,d\sigma\right] & t - t_k^+ < a \\ & t \in I_k^+. \end{cases} \tag{2.7}$$

Equation (2.7) is particularly nice as it gives a recursive formula relating the solution on I_{k+1}^+ to the solution on I_k^+.

Finally, it is important to note that should

$$n(t = t_k^+, 0) \neq n(t_k^+, a = 0) \tag{2.8}$$

then discontinuities will be propagated along all characteristics $\xi_k = 0$ for each k at which (2.8) is true.

From (2.7) we see that stochasticity occurs in the two integrals

$$\int_0^a \mu(t - a - t_k^+ + \sigma, \sigma)\,d\sigma \tag{2.9}$$

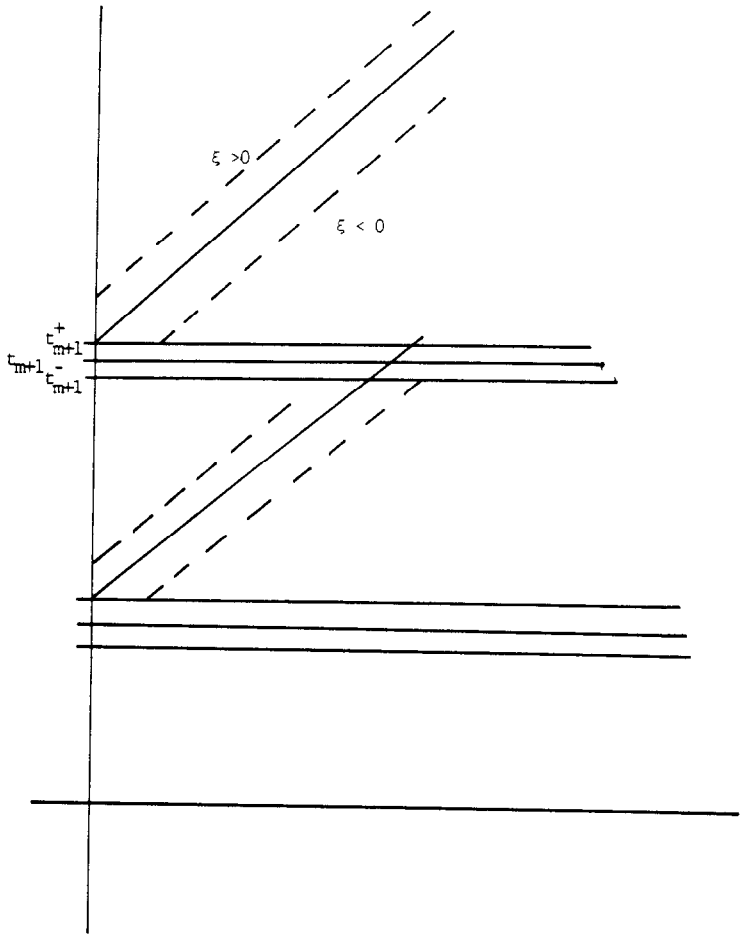

Fig. 2. An illustration of the characteristics for the integration of equation (2.4).

and

$$\int_{t_k^+}^{t} \mu(\sigma - t_k^+, \sigma - a - t)\, d\sigma. \tag{2.10}$$

From (2.1), these equations reduce to

$$\int_0^a \mu_1(\sigma)\mu_2(t - a - t_k^+ + \sigma)\, d\sigma \tag{2.11}$$

$$\int_{t_k^+}^{t} \mu_1(\sigma - a - t)\mu_2(\sigma - t_k^+)\, d\sigma. \tag{2.12}$$

Equation (2.11) requires that we integrate $\mu_2(t - a - t_k^+ + \sigma)$ over the interval $\sigma \in [0, a]$. This requires that we evaluate μ_2 on the interval $H_k^{(1)} = [t - a - t_k,\ t - t_k^+]$. For equation (2.12) we must evaluate μ_2 on the interval $H_k^{(2)} = [0, t - t_k^+]$.

On each interval I_k^+, $\mu(t)$ has value $\mu(t) = \mu_2(t_k) \forall t \in I_k^+$. Let $S_{k,n}^{(1)} = H_k^{(1)} \cap I_n^+ n = 0, 1, \ldots, k$. And let $S_{k,n}^{(2)} = H_k^{(2)} \cap I_n^+ n = 0, 1, \ldots, k$. On each set $S_{k,n}^{(i)} i = 1, 2$, $\mu(t)$ has value $\mu(t_k)$. Thus, we may write equations (2.11) and (2.12) as

$$\int_0^a \mu_1(\sigma)\mu_2(t - a - t_k^+ + \sigma)\, d\sigma = \sum_{n=0}^{k} \int_{S_{k,n}^{(1)}} \mu_1(\sigma)\mu_2(t_k)\, d\sigma \tag{2.13}$$

$$\int_{t_k^+}^{t} \mu_1(\sigma - a - t)\mu_2(\sigma - t_k^+)\, d\sigma = \sum_{n=0}^{k} \int_{S_{k,n}^{(2)}} \mu_1(\sigma - a - t)\mu_2(t_k)\, d\sigma. \tag{2.14}$$

A natural choice for the form of $\mu_2(t)$ would be one in which a deterministic mortality function, say $\mu_D(t)$, was perturbed by some stochastic function $\gamma(t)$. We might express this in the form $\mu_2(t) = \mu_D(t) + \gamma(t)$. In particular, one would not expect the deterministic mortality of a population to vary much in time. Consequently, it is natural to assume $\mu_2(t)$ to be of the form $\mu_2(t) = \mu_0 + \gamma(t)$ where μ_0 is a constant and $\gamma(t)$ is our random (slowly varying) process. This leads to equations of the form

$$\int_0^a \mu_1(\sigma)\mu_2(t-a-t_k^+ + \sigma)\,d\sigma = \sum_{n=0}^{k} \int_{S_{k,n}^{(1)}} [\mu_0 + \gamma(t_k)]\mu_1(\sigma)\,d\sigma \tag{2.15}$$

$$\int_{t_k^+}^{t} \mu_1(\sigma - a - t)\mu_2(\sigma - t_k^+)\,d\sigma = \sum_{n=0}^{k} \int_{S_{k,n}^{(2)}} [\mu_0 + \gamma(t_k)]\mu_1(\sigma - a - t)\,d\sigma. \tag{2.16}$$

Placing (2.15), (2.16) into (2.7) yields the new equation for $n(t, a)$

$$n(t,a) = \begin{cases} B(t-a-t_k^+)\exp\left[-\sum_{n=0}^{k}\int_{S_{k,n}^{(1)}} [\mu_0+\gamma(t_k)]\mu_1(\sigma)\,d\sigma\right] & t - t_k^+ > a \\ f[n(t_k^-, a)]\exp\left[-\sum_{n=0}^{k}\int_{S_{k,n}^{(2)}} [\mu_0+\gamma(t_k)]\mu_1(\sigma-a-t)\,d\sigma\right] & t - t_k^+ < a \\ & t \in I_k^+. \end{cases} \tag{2.17}$$

This approach may also be used to study the dynamics of (1.1) when the fertility function $\lambda(t, a)$ is a stochastic function of the form

$$\lambda(t, a) = \lambda_1(a)\lambda_2(t). \tag{2.18}$$

Following our previous discussion, let τ_k be an increasing sequence of times chosen small enough such that on each interval $J_n = [\tau_k, \tau_{k+1}]$ $\gamma(\tau_k)$ is a constant. From (2.4) we see that $\lambda(t, a)$ appears only in $B(t)$. Hence we need only consider the birth integral

$$B(t-a-\tau_k^+) = \int_0^\infty \lambda_1(a)\lambda_2(t-a-\tau_k^+)n(t-a-\tau_k^+, a)\,da. \tag{2.19}$$

As $a \in [0, \infty)$, $\lambda_2(t-a-\tau_k^+)$ is evaluated over the interval $G_k = (-\infty, t-\tau_k^+]$. Define the sets $T_{k,n}$ as follows:

$$T_{k,n} = G_k \cap J_n^+ \quad n = -\infty, \ldots, -3, -2, -1, 0, 1, 2, \ldots, k. \tag{2.20}$$

Equation (2.20) may then be approximated by

$$B(t-a-\tau_k^+) = \sum_{n=-\infty}^{k} \int_{T_{k,n}} \lambda_1(a)\lambda_2(\tau_n)n(t-a-\tau_k^+, a)\,da \quad t \in J_k^+. \tag{2.21}$$

Thus, for stochastic $\lambda(t, a)$ we obtain

$$n(t,a) = \begin{cases} \exp\left[-\int_0^a \mu(t-a-\tau_k^+ + \sigma, \sigma)\,d\sigma\right] \sum_{n=-\infty}^{k}\int_{T_{k,n}} \lambda_1(a)\lambda_2(\tau_n)n(t-a-\tau_k^+, a)\,da & t - \tau_k^+ > a \\ n(\tau_k^-, a)\exp\left[-\int_{\tau_k^-}^{t} \mu(\sigma-\tau_k^+, \sigma-a-t)\,d\sigma\right] & t - \tau_k^+ < a \\ & t \in J_k^+. \end{cases}$$

Clearly, we need not choose $\mu(t, a)$ or $\lambda(t, a)$ to be of the forms indicated in (2.1) or (2.18). The analysis for other forms would follow in a similar manner.

Finally, if we consider the case where both $\mu(t, a)$ and $\lambda(t, a)$ are stochastic functions in t we merely choose the smallest common partition which insures that the stochastic components of both the μ and λ functions are constant on pieces of the common partition.

3. APPLICATION TO CELLULAR MODELS

During the past decade, very substantial progress has been made in the critical testing of various alternative models and theories concerning the origins of the aging process. These advances come as a result of a variety of discoveries at the cellular, molecular, and integrative levels of function[8–13]. These advances bring credence to the current belief that many of the underlying causes for the loss of function in organs and in organ systems, with age, have their basis at the cellular level. Cellular loss of function with time would clearly result in multiple function lossess in humans; a fact which is quite elegantly documented in Martin[14].

This variety of experimental results on clonal senescence processes and mechanisms, expertly summarized in Martin[14], leads to a number of competing hypotheses/theories on mechanisms for aging in clonal cultures. An excellent review of these theories may be found in Good[15], Hayflick[16], and Comfort[17]. The mathematics of cell populations and aging in cell populations is reviewed in an extensive paper by Witten[2]. The results of this work are further discussed in Witten[5, 6, 18] and Cooke and Witten[19]. Any mathematical model of cellular aging must address the following well known biological data and questions:

Questions

How does one model a normal, non-pathological, asynchronously dividing cellular system[2, 5, 20, 21]?

In any model of an asynchronously dividing cellular system, how does one incorporate and describe mechanisms for the distribution of maternal properties to the daughter cells[8, 9, 11, 12, 23–31]?

How does one incorporate the known genetic and environmental factors, which affect the cell system, into such a model[13, 14, 32]?

How does one make use of such a model to recreate the clonal senescence results described in the literature[15, 21, 33–41]?

What combinations of the current aging hypotheses lead to more realistic results concerning senescence in cellular populations[37, 40]? And how can these results be extended to organs and organ systems[41, 42]?

Witten[2] has pointed out that one possible formalism for the study of cellular aging in human cellular systems is through a "sequential–dynamical" model which addresses the following two biological questions:

(1) At any time t, how many cells will enter mitosis?

(2) Once this population of cells has completed mitosis, how are the biological properties, denoted by the symbol Φ, passed along to the daughter cells?

Having a model which provides the answer to question (2) is not only useful in the study of aging effects, but is also useful in the study of cell kinetics and cancer therapy. Consider what has come to be known as Rubinow's Paradox (Thomas Lincoln, private communication). Here, the question involved is whether or not the inheritance of cell cycle times contributes to neoplastic selection and resistance. Rubinow's model, also called the maturity-time formulation of cell populations[43] realizes that cells mature, at a certain rate which is fixed until division. In Rubinow's Paradox, what is important is the question of the distribution of maturation rates (or cell cycle lengths) from mother cell to daughters; or mitotic portion $M(t; \Phi)$—the number of cells entering mitosis at time t and having collection of biological properties Φ—to daughter distribution $D(t; \Phi^*)$. For example, if one is discussing aging hypotheses, $\Phi = (\phi_1, \phi_2, \ldots \phi_n)$ might be a vector where ϕ_1 is the number of errors in the DNA synthesis machinery, ϕ_2 is the number of intracellular particles, and ϕ_n is the amount of membrane bound mitotic repressor.

A review of the literature[2, 5] shows that a historical choice of models for answering

question (1) has been a Von Foerster form, partial differential equation model[1, 43–49]. Using the results of such a formalism, one may determine the number of cells entering mitosis. The mitotic component of the model is then used to describe the distribution of mitotic properties to the daughters of the cells in $M(t, \phi)$. This result is then fed back to our population equations as a new initial condition. This is illustrated in Fig. 3.

Biologically, this type of formulation is quite reasonable. By means of an explanation, we begin with a culture plate. We will assume that we are looking at a plate, for ease of explanation. This culture plate contains a distribution of cells carrying certain properties that we wish to measure or to keep track of. At each instant t, *some* of the cells $M(t; \Phi)$ on the plate will commence mitosis. At time Δt later, there will be two distributions of cells on the plate: (i) the cells that did not divide in the time interval $(t, t+\Delta t)$; and (ii) the daughter distribution of those cells that did undergo a mitotic event in this time interval. Effectively, this is a *new* culture plate, and the growth dynamics of the system must be readjusted to this new starting configuration. Thus, what we are looking at is a cellular level sequential–dynamical system. This system is illustrated in Fig. 4, where we describe the passage of an intracellular particle. Figure 4 illustrates the dynamics for both the mitotic and non-mitotic components of the cellular population in this problem.

Extension and further formalization of this formalism may be found in Witten[5, 6]. Witten has pointed out that, in order to more realistically analyze cellular senescence, it is necessary to compartmentalize the cellular system (in a preliminary and simplistic manner) into five cell compartments: (i) Those cells which have been affected by the environment or genetic factors and are able to undergo a mitotic event; (ii) Those cells that have become IND as a consequence environmental factors, where IND denotes Irreversibly Non-Dividing; (iii) Those cells that have been shut down temporarily by the environment (environmentally statelocked), but may be activated at some future time and; (iv) Those cells that have become IND as a consequence of genetic factors and; (v) Those cells that have become statelocked by genetic factors, but which may become activated at some future time; where each compartment has an equation describing the dynamical behavior of that compartment. We first illustrate a simplified version of the final model in which a Von Foerster equation is used as the compartment

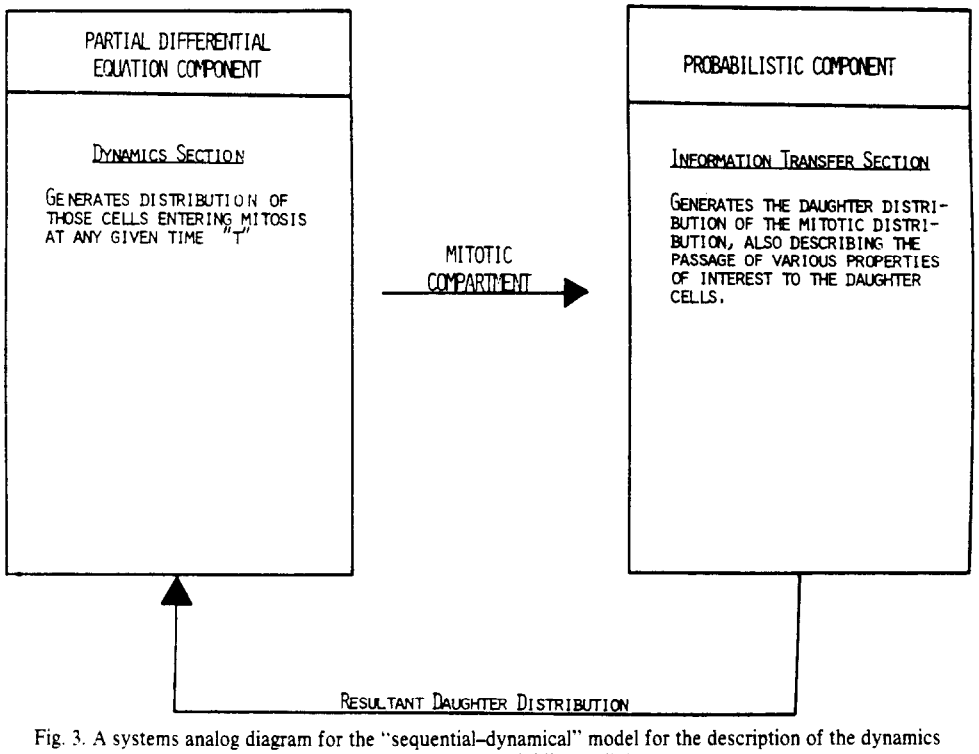

Fig. 3. A systems analog diagram for the "sequential–dynamical" model for the description of the dynamics of a normal, asynchronously dividing, cellular system.

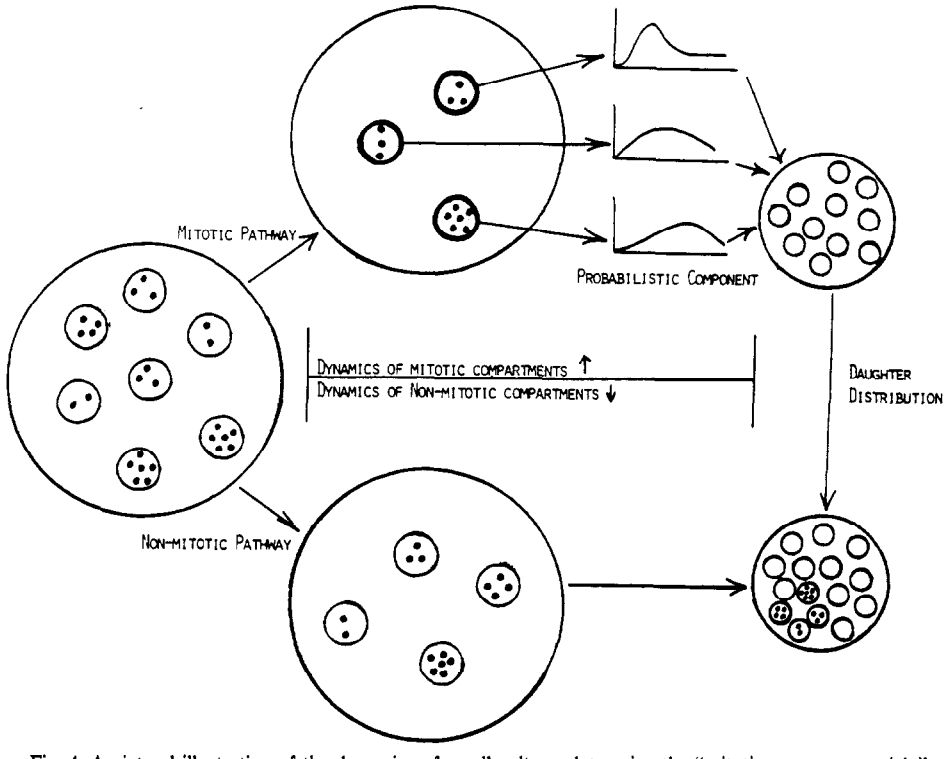

Fig. 4. A pictoral illustration of the dynamics of a cell culture plate using the "mitotic repressor particle" theory of cellular aging.

equation. The general age-time, cell cycle model, for a one compartment population has the form.

$$\begin{cases} \dfrac{\partial n}{\partial a}+\dfrac{\partial n}{\partial s}+\dfrac{\partial n}{\partial t}=-\mu(a,t,s,n)n(a,t,s) \\ n(a,s,t=0)=n_0(a,s) \\ n(0,t,0)=\displaystyle\iint \lambda(a,t,n)n(a,t,T)\,da\,dT. \end{cases} \tag{3.1}$$

For details see Lincoln *et al.* (48). This system would be replaced by the new system

$$\begin{cases} \dfrac{\partial n}{\partial a}+\dfrac{\partial n}{\partial s}+\dfrac{\partial n}{\partial t}=-\mu(a,t,s,n)n(a,t,s) \quad s\in[0,T] \\ n(a,s,t=0)=n_0(a,s) \\ n(0,0,t^+)=f[n(a^-,t^-,T)] \\ n(a^+,s^+,t^+)=\begin{cases} n(a^-,t^-,s^-)-n(a^-,t^-,T) & s^-=T \\ n(a^-,t^-,s^-) & s^-\neq T \end{cases} \end{cases} \tag{3.2}$$

where $f[n(a^-,t^-,T)]$ is the probability distribution acting upon $n(a^-,t^-,T)$ the mitotic component of the population. The form of $f[\ ]$ is currently unknown. Estimates based upon consultation and literature must be made and fitted to the experimental data. The advent of spectrocytofluorometric methods has made a significant increase in the availability of accurate and detailed cellular data.

In order to apply the methodology of Section II, let us consider the slightly simplified

system

$$\begin{cases} \dfrac{\partial n}{\mu s}+\dfrac{\partial n}{\mu t}=-\mu n(t,s) \quad \mu \text{ constant}, \quad s\in[0,T] & (3.3a)\\ n(t_k^+,0)=kn(t_k^-,T) \quad k \text{ constant} & (3.3b)\\ n(t_k^+,s_k^+)=\begin{cases} n(t_k^-,s_k^-)-n(t_k^-,T) & s_k^-=T\\ n(t_k^-,s_k^-) & s_k^-\neq T\end{cases} & (3.3c)\\ n(0,s)=n_0(s) & (3.3d)\end{cases}$$

where t_k^-, t_k, t_k^+ is an increasing sequence of times (the t_k may be times at which the system is observed) satisfying

$$\begin{aligned}&\lim_{t\downarrow t_k^+} n(t_k^+,s)=n(t_k,s)\\ &\lim_{t\uparrow t_k^-} n(t_k^-,s)=n(t_k,s).\end{aligned} \tag{3.4}$$

In this case, we may solve for $n(t,s)$ on $I_k^+=(t_k^+,t_{k+1}^-)$ (from (3.3a)) and use (3.3d) as our initial condition. Equations (3.3b, c) describe the distribution as one transits from I_k^+ to I_{k+1}^+ (adjacent intervals).

Witten (5) has discussed the application of the Rubinow (43) maturity time formulation to the problem of cellular senescence models. This leads to a model of the form

$$\begin{cases} \dfrac{\partial N(\mu,t)}{\partial t}+\dfrac{\partial(vN)}{\partial \mu}=-\lambda N \quad \mu_0\leqq\mu\leqq\mu_F\\ N(\mu,t=0)=g_0(\mu)\\ N(\mu_0,t^+)=f[N(\mu,t^-)]\\ N(\mu^+,t^+)=\begin{cases} N(\mu^-,t^-)-N(\mu_F,t^-) & \mu^-=\mu_F\\ N(\mu^-,t^-) & \mu^-\neq\mu_F\end{cases}\end{cases} \tag{3.5}$$

where v is the maturation velocity, and μ is the maturity. This formulation represents a single cell compartment in which a sequential mitotic process is occurring while a continuous dynamical maturation process is ongoing.

Finally, there may be transitions between the compartments in this simple model. Hence, let $i=1$ be the mitotic compartment and $i=2$ be the genetically irreversibly nondividing compartment. Further, is we use Rubinow driver equations to model the population dynamics we obtain the following mitotic and genetically IND compartment models

$$\begin{cases} N_t^{(1)}+(vN)_\mu^{(1)}=-\lambda^{(1)}N^{(1)}\\ N^{(1)}(\mu,t=0)=g_0^{(1)}(\mu)\\ N^{(1)}(\mu_0,t^+)=f^{(1)}[N^{(1)}(\mu_F^{(1)},t^-)]\\ N^{(1)}(\mu^+,t^+)=\begin{cases} N^{(1)}(\mu^-,t^-)-N^{(1)}(\mu_F^{(1)},t^-) & \mu^-=\mu_F^{(1)}\\ N^{(1)}(\mu^-,t^-) & \mu^-\neq\mu_F^{(1)}\end{cases}\end{cases} \tag{3.6}$$

$-$ transitions to compartments $i=2, 3, 4,$ and 5
$+$ transitions from compartments $i=4, 5$.

$$\begin{cases} N_t^{(2)}+(vN)_\mu^{(2)}=-\lambda^{(2)}N^{(2)}\\ N^{(2)}(\mu,t=0)=g_0^{(2)}(\mu)\\ N^{(2)}(\mu_0,t^+)=f^{(2)}[N^{(2)}(\mu_F^{(2)},t^-)]\\ N^{(2)}(\mu^+,t^+)=\begin{cases} N^{(2)}(\mu^-,t^-)-N^{(2)}(\mu_F^{(2)},t^-) & \mu^-=\mu_F^{(2)}\\ N^{(2)}(\mu^-,t^-) & \mu^-\neq\mu_F^{(2)}\end{cases}\end{cases} \tag{3.7}$$

$+$ transitions to compartments $i=1, 4, 5$

where $i = 3$ corresponds to environmentally induced irreversibly non-dividing cells, $i = 4$ corresponds to genetically statelocked cells, and $i = 5$ corresponds to environmentally statelocked cells. Preliminary results on the existence of solutions to such systems are forthcoming.

In closing this section we should note an important fact. The idealization of an asynchronously dividing cellular systems into the five compartments discussed in this portion of the paper is certainly an oversimplfication of a cellular system. It is clear that cells need not reside in any one of the given compartments at any given time. And, in point of fact, certain compartments may not be present in this formulation. Further, certain cellular systems may have cells which simultaneously reside in more than one compartment. These are valid objections. However, their inclusion would introduce further complexity into the analysis of a model which is quite complex at present. Thus, we choose to temporarily ignore them in this paper.

4. CLOSING REMARKS

We have seen how naturally occuring stochasticity may be incorporated into the age-time Von Foerster partial differential equation. And, under certain assumptions—namely that the stochastic terms not fluctuate too rapidly in time—we have seen how the solution to the Von Foerster system may be constructed. We have seen this formalism dovetails very naturally with the concepts of "sequential-dynamical" partial differential equation systems. In particular, we investigate how one may use the concepts of slowly varying stochastic systems to analyze the problem of modeling a normal, asynchronously dividing cellular system.

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